Biomarkers and prediction models for type 2 diabetes and diabetes related outcomes

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Summary

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Type 2 diabetes (T2D) and its micro- and macro-vascular causes are an increasing global health burden. In addition, the prevalence of obesity and T2D are shifting to younger ages, increasing the burden of T2D and diabetes-associated co-morbidities, including cardiovascular disease (CVD) and renal disease. Given chronicity and preventability of diabetes and its complications, early identification of high-risk individuals for future outcomes is essential for targeted preventive strategies. This approach is beneficial to avoid the burden of intervention on both low-risk individuals and to limit healthcare resources. To estimate risk of future outcome, the use of a reliable and practical scoring tool/questionnaire is recommended. Of course, a valid tool can also help to inform the patient about the future – expected – course of their illness, and can guide doctors and patients in decisions on further treatment.

Many tools for prediction of type 2 diabetes and its complications are available. Current tools need validation for use in other populations as well as regular updating due to changes in treatment and clinical characteristics. Addition of novel biological clues (i.e. biomarkers) can be of value to increase the predictive power or to increase the specificity of prediction of CVD and renal complications of diabetes.

We first conducted a systematic review to retrieve the most relevant existing models for predicting the risk of future T2D. Then, we used various analytical measures for validating and comparing their predictive performance in a large Dutch population (**Chapter 2**). We showed that most of current risk scores are valid tools to discriminate between high-risk and low-risk individuals within 5 to 10 years. However, most of these risk scores overestimated the absolute risk of diabetes in our validation study. We found that the calibration of such risk scores can be improved when they are adjusted for differences (e.g. incidence of outcome or effect size for predictors) between the original setting and new circumstance before use in practice.

Second, In **Chapters 3, 4** and **8**, we performed analyses in sex-stratified subgroups to account for potential sex differences in the prediction performance of models and incremental predictive value of liver function tests. We showed that existing prediction models such as KORA have a slightly better discrimination performance to identify women than men at high risk for T2D (**Chapters 3** and **4**). Subsequently, we found a statistically significant improvement in prediction only in men when we added liver function tests to the KORA model incorporating glucose, uric acid plus HbA1c. Next, we found that the positive association between copeptin, as a stress-system marker, and the risk of developing T2D was stronger in women than in men (**Chapter 8**). In fact, addition of copeptin to the DESIR model significantly improved prediction of diabetes only in women. Therefore, it is particularly important to take into account the possible sex differences for the assessment of the value of biomarkers (**Chapter 8**).

In **Chapters 7**, **9** and **10**, we have evaluated lipids and inflammatory markers (C-reactive protein and procalcitonin) for their associations with the metabolic syndrome and risk of incident T2D. **Chapter 9** describes the inverse relationships of HDL-cholesterol, HDL-cholesterol/apoA-I and HDL-cholesterol/apoA-II ratios with

incident T2D (as estimates of HDL particle composition). We observed that the associations were independent of other metabolic syndrome components, including (central) obesity, hypertension, fasting plasma glucose and triglycerides, as well as of a positive family history of diabetes. The study described in **Chapter 7** determined that variation in plasma procalcitonin within the normal range is positively associated with insulin resistance and the metabolic syndrome in apparently healthy men and women. The association of plasma procalcitonin with insulin resistance and the metabolic syndrome was independent of age, measures of obesity, CRP, history of cardiovascular disease and health behaviors (**Chapter 7**). Moreover, we found plasma procalcitonin to be an independent predictor of incident T2D. Particularly, plasma procalcitonin was more strongly associated with incident T2D than CRP after accounting for adiposity (**Chapters 10**). After addition of procalcitonin to the DESIR clinical equation, we observed 1% increase in discriminative power to predict T2D while this was not significant for CRP. In **Chapter 11**, we describe our findings concerning the relation of peroxiredoxin 4 (Prx4), a novel circulating biomarker for oxidative stress, with future risk of CVD on top of classic risk factors included in the Framingham risk score (FRS). In a Cox-regression model adjusted for the Framingham risk factors, the marker seemed promising, but, after addition of Prx4 to the FRS, the incremental predictive value for 10-year risk of CVD was marginal (2.7% net reclassification improvement).

There are some potential explanations for the limited additive value of biomarkers that have been studied so far. First, biomarker levels overlap between cases and non-cases, limiting their incremental predictive value. Second, most testable biomarkers are in the causal biological pathways leading to disease or are a consequence of the disease and share associations with cardiometabolic disorders such as adiposity, hypertension and diabetes. Because of the resulting correlations between diabetes risk factors such as family history of diabetes and biomarkers, addition of inflammatory or stress biomarkers to conventional risk factors will only provide small improvement in prediction for risk of T2D.

In summary, this thesis shows that many prediction models have been developed for risk of future T2D. Nevertheless, studies which compare validity and performance of available diabetes risk scores using high-quality prospective data are still ongoing. Steps to be undertaken are to validate and to compare multiple risk scores in prospective cohorts, to update the best fitted model for the situation of interest, clinical practice vs. public health care. Additionally, a long journey starts with further investigations to evaluate the predictive value of abundant biomarkers becoming available beyond that of the common diabetes risk factors. The increasing availability of computers and internet in clinical practice may allow for these more sophisticated and potentially better risk scores. At the same time, this can be a disadvantage and good prediction models based on clinical data are valid to identify high-risk individuals at 5-10 years; however, they can not sufficiently quantify absolute risk of future T2D. We also explored associations of novel risk factors, such as inflammatory, stress system and oxidative stress biomarkers, with risk of T2D,

obesity, kidney function and CVD. Addition of novel biomarkers to validated tools can lead to small to modest improvement in prediction of T2D and CVD. Future studies are warranted to estimate risk of T2D and its complications over the lifetime.